PFAS (perfluoroalkyl and polyfluoroalkyl substances) and breast cancer

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Peer reviewed by two members of Breast Cancer UK independent Science Panel

1. Summary

PFAS comprise a large class of synthetic compounds that contain carbon-fluorine bonds. They have heat-resistant, non-stick and water-repellent properties and are used widely in food packaging, textiles, non-stick cookware, cosmetics and fire-fighting foam. They degrade very slowly and are distributed globally. PFAS are found in body fluids and tissues, for example, blood, breast milk and placenta. They are associated with many health problems, including cancer, and may increase breast cancer risk. Animal studies have shown that PFAS exposure may increase the risk of mammary tumours, and in utero (i.e. in the womb), exposure may affect mammary gland development. In vitro, PFAS increase human breast cell proliferation and migration. Elevated serum levels of PFAS in humans may be associated with increased breast cancer risk. Some PFAS are banned due to their persistence and health effects. Those in current use are also persistent and likely to be harmful. Breast Cancer UK supports a ban on all non-essential use of PFAS.

2. Introduction

Polyfluoroalkyl and perfluoroalkyl substances, or "PFAS", are a large group of over 9,000 synthetic chemicals [1] used since the 1940s in consumer and industrial products [2]. They are versatile compounds with heat-resistant, non-stick, stain-resistant, grease-proof and water-repellent properties.

PFAS are highly stable due to their carbon-fluorine bonds. All are persistent In the environment or else break down into other persistent PFAS [3]. As such, they are often called "forever chemicals". PFAS are mobile and have become widespread in the soil, water, sediment and air. Many bioaccumulate

Glossary box:

Bioaccumulation: build-up of one or more chemicals in the body.

Epidemiological studies: are conducted on a group of individuals (population) to investigate the possible link between a risk factor and a disease.

Epigenetic modifications: alteration to the expression of genes, but not the DNA sequence, that can be inherited from a parent or grandparent.

Half-life: the time required to reduce by half the amount of a chemical in the body.

In utero: Latin term for "in the womb".

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in wildlife and humans and are associated with detrimental health effects [3–5], including cancer [6,7]. Several PFAS have been banned due to their impact on human health and the environment. Less is known about replacement PFAS, although there is increasing evidence that these are also persistent and harmful [4].

Breast cancer is the most common cancer globally [8]. In the UK, around 55,500 women and 400 men are diagnosed with the disease annually [9]. Numerous factors, e.g. age, gender, diet, lifestyle and exposure to harmful chemicals, affect an individual's risk of developing this disease [10]. There is increasing evidence that exposure to certain PFAS may increase breast cancer risk [11]. This review will discuss PFAS and their impacts on human health and the environment, focusing on their potential role in breast cancer.

3. PFAS chemistry

The Organisation for Economic Co-operation and Development (OECD) defines PFAS as "fluorinated substances that contain at least one fully fluorinated methyl ($-CF_3$) or methylene ($-CF_2-$) carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated* methyl group ($-CF_3$) or a perfluorinated methylene group ($-CF_2-$) is a PFAS" [12].

PFAS consist of carbon chains of different chain lengths where the hydrogen atoms are completely ("per") or partially ("poly") replaced by fluorine atoms. Those with repeated chains are "polymers" [13]. Appendix 1 describes PFAS groupings, and Table 1 includes the full names of PFAS discussed in this review (which uses abbreviated names) and where they are used.

Glossary box (cont.):

In vitro studies: also known as "test-tube experiments", are lab-based studies conducted with cells or biological molecules and not in a living organism.

In vivo studies: are conducted in living organisms, usually animals, humans or plants.

Meta-analysis: statistical analysis of multiple published scientific studies.

The most studied PFAS are the perfluoroalkylated acids (PFAAs), which comprise long or short chains of carbon-fluorine groups. Long-chain perfluoroalkyl carboxylic acids (PFCAs) are defined as having an 8-carbon alkyl chain or longer, for example, perfluorooctanoic acid (PFOA). Long-chain perfluoroalkyl sulfonic acids have a perfluoroalkyl chain of 6 carbons or longer and include perflurooctane sulfonic acid (PFOS). Most studies focus on two long-chain PFAAs, PFOA and PFOS (Figure 1).

The hazardous nature of PFOS and PFOA was recognised in the early 2000s, and their use has since been phased out in many countries, including the UK [14]; PFOS, its salts and PFOSF were added to Annex B of the UN Stockholm Convention for persistent organic pollutants (POPs). PFOA was added to Annex A in 2019, and another

*perfluorinated refers to a hydrocarbon where the hydrogen atom is replaced with fluorine.

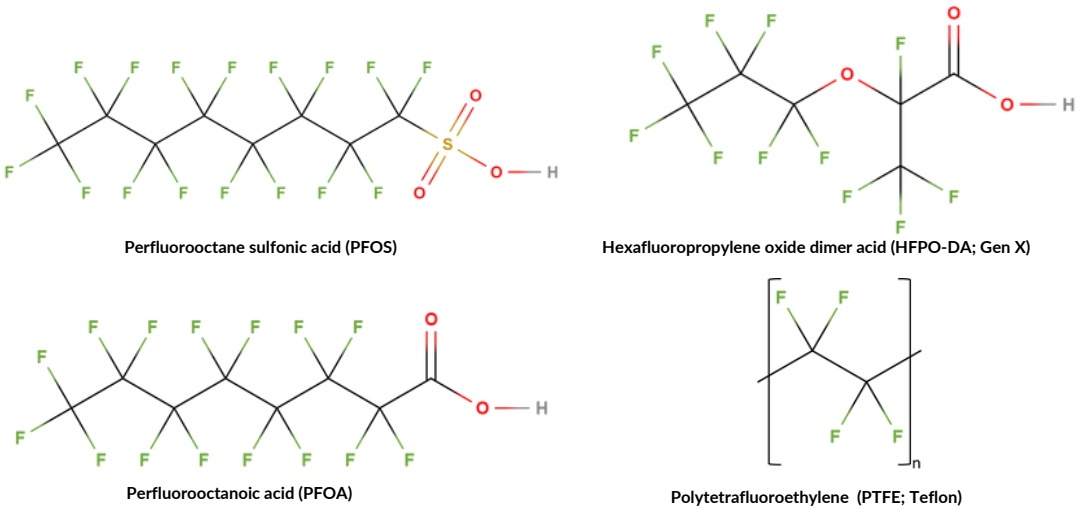

Figure 1. Chemical structures of the legacy PFOS, PFOA, the polymer PTFE and the emerging HFPO-DA (also known as GenX). Image created in MolView.

long-chain PFAA, PFHxS, was added to Annex A in 2022 [15]. These are referred to as "legacy" PFAS, defined as long-chain PFAAs (and precursors) that have been phased out of production in numerous developed nations [4]. The POPs review committee is currently evaluating long-chain PFCAs with carbon chain lengths from 9 to 21 (and their salts) [16].

Legacy PFAS have been replaced by "emerging" PFAS, which include short-chain PFAAs and perfluoroalkyl ether acids (PFEAs) such as HFPO-DA (Figure 1) [5]. Although short-chain PFAS are often considered less hazardous due to their shorter half-lives (the time it takes for a quantity of substance to break down to half its initial value), evidence is emerging that they are also persistent and harmful [5]. Short-chain PFAS are more hydrophilic and often present in surface waters, whereas long-chain PFAS are more hydrophobic and are more often found in sediments [17].

A well-known example of a PFAS polymer is PTFE or Teflon (Figure 1). Previously, such fluoropolymers were not considered harmful. However, PFOA (or other PFAS) used to make Teflon may be released during production, use (e.g. when cookware is damaged), or disposal [18]. Similarly, other short- and long-chain PFAS may arise due to the degradation of more complex PFAS. The end degradation products are typically PFAAs, resistant to further degradation [2].

4. Where are PFAS used?

PFAS are used in a wide range of industrial processes and consumer products. A 2020 study identified over 200 different uses involving over 1,400 individual PFAS [19]. Their main applications are in protective treatments, polymer manufacturing and as surfactants [2].

Non-polymeric PFAS are used in the building industry and electrical and electronic equipment, gas and air conditioning, pesticides, and cleaning products. They are also found in aqueous film-forming foam (AFFF) used

Table 1. Description of PFAS referred to in this review [1, 2, 19].
Abbreviations: PFAA: perfluoroalkyl acid; PFCA: perfluoroalkyl carboxylic acid; PFSA: perfluoroalkyl sulfonic acid; PFEA: perfluoroalkyl ether acids. SVHC (UK REACH): Substance of Very High Concern under UK REACH. POP: persistent organic pollutant. AFFF: aqueous film-forming foam. PFAS in red may be described as legacy PFAS; those in blue are emerging PFAS [4].

Acronym	Full chemical name	Type of PFAS and UK regulation	Examples of use & products that contain
Non-polymeric PFAS: perfluoroalkyl substances			
PFOS	perfluorooctane sulfonic acid	PFAA; long-chain PFSA Annex A POP; began phase out 2000s	General coatings, mist suppressants for metal plating applications, AFFFs, textiles, leather goods, paper packaging, food contact materials
PFOSF	perflurooctane sulfonyl fluoride	Perfluoroalkane sulfonyl fluoride Annex B POP; began phase out 2000s	PFOS precursor for perfluorinated amides, alcohols, acrylates and other fluorochemical polymers, surfactant
PFOSA (FOSA)	perfluorooctane sulfonamide	Perfluoroalkane sulfonamide PFOS precursor; breaks down to PFOS began phase out 2000s	Precursor for AFFFs, surfactants (cleaners, polishers), pesticide ingredient, coatings for textiles and paper, insecticide formulation
PFOA	perfluorooctanoic acid	PFAA; long-chain PFCA Annex A POP; Began phase out 2000s SVHC (UK REACH)	Originally a replacement for PFOS; fluoropolymer manufacture, AFFFs, inks, coatings, surfactants, greases, water & oil proofing for textiles, cosmetics
PFHxS (PFHS)	perfluorohexane sulfonic acid	PFAA; long-chain PFSA Annex A POP; SVHC (UK REACH)	Mainly as a raw material or precursor for production of perfluoroalkyl sulfonate-based products; manufacturing of electronics, metal plating, AFFFs, textiles, leather, surfactants, inks, paints, waxes
PFNA	perfluorononanoic acid	PFAA; long-chain PFCA; began phase out 2000s; SVHC (UK REACH)	Surfactants, manufacturing of electronics, textiles and leather, paper and packaging, inks, paints, waxes
PFDA	perfluorodecanoic acid	PFAA; long-chain PFCA; SVHC (UK REACH)	Surfactants, wetting agent, AFFFs, textiles, leather, paper & food packaging, inks, paints, waxes, polishes, cosmetics
PFUnA	perfluoroundeca-noic acid	PFAA; long-chain PFCA; SVHC (UK REACH)	Surfactants, polishes, AFFFs, textiles, leather, paper and food packaging, inks, paints, waxes, cosmetics
PFDoA	perfluorododecanoic acid	PFAA; long-chain PFCA; SVHC (UK REACH)	Surfactants, polishes, AFFFs, textiles, leather, paper and food packaging, inks, paints, waxes, cosmetics
HFPO-TA	hexafluoropropylene oxide trimer acid	long-chain PFEA	PFOA alternative in fluoropolymer production (processing aid for PTFE and PVDE (vinylidene fluoride)

Table 1 (cont.). Description of PFAS referred to in this review [1, 2, 19].

Acronym	Full chemical name	Type of PFAS and UK regulation	Examples of use & products that contain
HFPO-TeA	hexafluoropropylene oxide tetramer acid	long-chain PFEA	PFOA alternative in fluoropolymer production (e.g. PTFE)
PFPeA	perfluoropentanoic acid	PFAA; short-chain PFCA	Production of fluoropolymers, surfactants, AFFFs, textiles, chipboard, cosmetics, ski wax
PFHpA	perfluorohepta-noic acid	PFAA; short-chain PFCA	Production of fluoropolymers stain or water repellent, AFFFs, food packaging materials, cosmetics
PFHxA	perfluorohexanoic acid	PFAA; short-chain PFCA	Mist suppressants for metal plating applications, manufacturing of electronics; stain resistant finish surfactants, textiles, leather, AFFFs, inks, paints, waxes
PFBS	perfluorobutane sulfonic acid	PFAA; short-chain PFSA	surfactant; emulsifier; dispersive; used as a stain or water repellent, polishes, AFFFs; PFOS replacement in Scotchguard
PFBA	perfluorobutanoic acid	PFAA; short-chain PFCA	Wetting, dispersing, emulsifying, and foaming agents paints, waxes, AFFFs, circuit boards, cosmetics, leather food packaging, cosmetics
HFPO-DA (GenX)	hexafluoropropylene oxide-dimer acid	short-chain PFEA; SVHC (UK REACH)	Processing aid for manufacture of fluoropolymers e.g. PTFE, chrome plating; substitute for PFOA
Non-polymeric PFAS: polyfluoroalkyl substances			
6:2 Cl-PFESA (F-53B)	chlorinated polyfluoroalkyl ether sulfonate	Chloropolyfluoroalkyl ether acid	PFOS alternative in electroplating industry; mist suppressant in chrome plating
8:2-FTOH	8:2 fluorotelomer alcohol	Fluorotelomer	Raw materials in production of fluorotelomers & polymers, surfactants, stain- & water-resistant textiles, paper, dental floss, grease proof paper, sealants, AFFFs; metabolised to PFCA
6:2-FTOH	6:2 fluorotelomer alcohol	Fluorotelomer	Raw materials in production of fluorotelomers; stain- and water-resistant textiles, dental floss, lubricants, grease-proof paper, AFFFs; metabolised to PFCA
Polymers			
PTFE (Teflon)	polytetrafluoro ethylene	Fluoropolymer	Electrical equipment, filaments, medical devices e.g. heart valves; aerospace industry, electrical wiring; non-stick cookware; seals, textile coatings for glass, fabrics, linings, seals, tubing, membranes; PFOA was originally used as a precursor in PTFE production, but is no longer used in most countries.

to tackle fires. Such foams often contain complex mixtures of PFAS and other environmental contaminants, such as brominated flame retardants [20,21]. PFAS polymers are used in paints, lubricants and greases, in producing plastic, rubber, and the chemical industry.

Consumer products where PFAS are commonly found include paper and cardboard food packaging, waterproof textiles such as carpets, cosmetics and personal care products (e.g. dental floss), contact lenses, waxes, fishing lines, pesticides, batteries, smartphones, paint and non-stick cookware [19,22].

5. Exposure to PFAS

Humans and wildlife are primarily exposed to PFAS by consuming contaminated food and drinking water [23]. Exposure also occurs via air and dust. People may also be exposed through skin contact with PFAS-treated clothes, textiles, or cosmetics [2].

PFAS are released into the environment from waste-water effluent, landfills, recycling and incineration plants, following the application of sewage sludge to soil and from industrial facilities that produce, process or use PFAS in manufacturing [2,3]. Military bases, airfields, fire stations, and fire-fighting training sites that use AFF are also major point sources of PFAS contamination [2].

Food may contain high levels of PFAS. According to the European Food Safety Authority (EFSA) (2018), the highest levels of PFOS and PFOA are found in meat and meat products [24]. High levels are also present in fish and other seafood. The UK Environment Agency monitoring shows a widespread presence of PFOS in both freshwater and marine fish from English waters [2]. Other important food sources include dairy products and eggs [24]. PFAS also accumulate in vegetables, especially when grown in contaminated soil [25].

Food contamination also occurs as a result of migration of PFAS from food packaging and non-stick coatings on cookware [24,26]. PFAS are used in cardboard and paper packaging to provide resistance to oil, water and fat. A UK study in 2020 carried out by Fidra found that around 30% of 92 samples of UK food packaging from supermarkets and takeaway outlets were likely to contain PFAS [27]. Some UK supermarkets and food chains have committed to removing PFAS from their own brand packaging [28].

Globally, PFAS are routinely detected in oceans, surface water, groundwater and drinking water. In the United States, one survey found levels of PFOA and PFOS that exceeded the US Environmental Protection Agency's (EPA's) minimum reporting levels were being supplied to 16 million US residents [29]. Sources near sites where PFAS were manufactured or used, wastewater treatment plants and where AFFF was used regularly had particularly high levels [29].

Water monitoring by the UK Environment Agency between 2014 and 2019 identified PFOS and PFOA as widespread contaminants in surface

waters [2]. Short-chain PFAAs (PFBS, PFHxA, PFPeA and PFHpA) and PFHxS, which are more mobile, are frequently detected in surface and ground waters.

Cosmetics and personal care products often contain PFAS. A 2022 survey by the Danish Consumer Council THINK investigated ingredients in 13,000 cosmetics and personal care products and identified 91 products from 30 brands containing PFAS [30]. According to the Cosmetic Toiletry and Perfumery Association (CTPA), nine different PFAS are used in this sector in the UK, mostly to make cosmetics easier to apply or more water resistant [31]. Although not a major human exposure route, PFAS from personal care products can be absorbed through the skin [23]. Dermal exposure to PFAS substitutes, such as PFHxA, can induce toxicity in animals [32].

PFAS can be transferred to the foetus through the placenta, and infants are potentially exposed to PFAS through breast milk [33,34]. Breastfeeding may be a significant exposure route for infants whose mothers had high exposures to PFAS from contaminated drinking water [35]. You can read more about breastfeeding here.

6. Biomonitoring of PFAS

PFAS have been found in the blood of over 330 different wildlife species, including polar bears, whales, pandas, horses, cats, squirrels and frogs [23,36] and are routinely detected in human blood [4]. The Center for Disease Control (CDC) has been monitoring serum levels of at least 12 different PFAS in the US population since 1999 and has found PFOA, PFOS, PFHxS and PFNA in over 99% of the sampled US population [37].

The EU's HBM4EU project included biomonitoring of 12 PFAS in the serum of European teenagers. Overall, 14% of participants exceeded the EFSA health-based guidance for combined exposure to PFOS, PFOA, PFNA and PFHxS, with higher levels of PFNA and PFOS associated with more frequent consumption of fish, seafood, offal and eggs [38].

Few biomonitoring studies have been conducted in UK populations [1]. One study that examined serum levels of PFOS, PFOA, PFHxS, and PFNA in 457 pregnant women found PFAS in all samples [39]. Currently, the Health Survey for England collects urine and blood samples for PFAS analysis, with results expected in 2024 [1].

Levels of legacy PFAS† in Western and Japanese populations are decreasing as these compounds are being phased out. Levels of replacement PFAS, such as short-chain PFAAs, are increasing [4,23,40,41].

Individuals exposed to PFAS-contaminated drinking water have raised levels of PFAS in their blood [42]. Due to occupational exposures, fluorochemical plant workers, professional ski waxers, firefighters and chrome plating factory workers have higher PFAS serum levels [43–45].

†Legacy refers to compounds no longer in use in most countries, including the UK, however legacy compounds such as PFOA are still manufactured and used in some countries.

Many PFAS are substrates for transport proteins, such as serum albumin, which help facilitate their entry into cells. PFAS accumulates in tissues such as blood, liver, kidneys, and brain [46]. They have been measured in urine, breast milk, muscle [46], follicular fluid [47], placenta [48] and human foetus [49].

Long-chain PFAS remain in the body for many years; for example, PFOA has an elimination half-life of 2-10 years. In comparison, short-chain PFAS are excreted more rapidly; for instance, PFBA has an elimination half-life of around three days [50]. Long-chain PFAS thus have a higher potential to bioaccumulate [46].

The main route of removal of PFAAs is through the kidneys, with some removal through menstruation, pregnancy, and lactation. As a result, women have lower serum levels of PFAS compared to men [51]. Most PFAS are excreted in their original form [7].

7. Effects of PFAS on human health

Studies in humans have observed a link between elevated serum levels of PFOA and kidney and testicular cancer [6]. Other epidemiological studies in humans have identified possible links to other cancers, including thyroid, prostate, bladder, ovarian and breast cancer (see below), although results are not conclusive [4].

Epidemiological studies also suggest legacy PFAS can disrupt menstruation [51], affect semen quality and sperm count [52] as well as reduce breastfeeding duration [53]. Exposure during pregnancy is associated with pregnancy-induced hypertension and may result in low infant birth weight and disruption of developmental processes, including breast tissue development [54]. PFAS are also linked to thyroid disease, elevated serum cholesterol, ulcerative colitis and immunotoxicity [4]. Children with elevated serum PFAS (PFOA, PFOS, PFHxS) show reduced antibody response following vaccination and children whose mothers had elevated serum PFOS may have an increased number of infections [55].

Several legacies and emerging PFAS are known or suspected endocrine disrupting chemicals (EDCs) [56]. Endocrine disruption of sex hormones, especially oestrogen, may increase breast cancer risk [56]. Elevated exposure to natural oestrogen is an established breast cancer risk factor.

EDCs that modulate the actions of oestrogen are described as oestrogenic. Non-oestrogenic EDCs may also affect human breast carcinogenesis [57]. In utero, exposures to EDCs are particularly harmful [58].

PFAS may disrupt oestrogen [59], progesterone [60] and thyroid [61] hormones. In vitro, studies have shown that PFAS can bind to peroxisome proliferator-activated receptors (PPARs), which regulate pathways associated with the cell cycle, energy production, lipid metabolism and inflammation [51], and to pregnane X receptor, which is

associated with cell proliferation and migration [62].

In animal studies, PFAS, when in mixtures, has displayed dose additive toxic effects [63,64]. In these studies, pregnant rats were exposed to more than one PFAS, and the observed toxic effects were dose additive in both mothers and offspring. This is due to different PFAS having similar toxic effects; thus, the toxicity of a PFAS mixture is given by the combination of the dose and potency of each mixture component.

8. PFAS and breast cancer

Evidence based on in vitro, in vivo and epidemiological studies suggests exposure to PFAS increases breast cancer risk, although an association has not been confirmed [11].

Most studies show that exposure to low levels of PFAS does not damage DNA directly [7], although exposure to high levels can cause DNA damage through the generation of reactive oxygen species [65]. The carcinogenic effects of PFAS are likely to be associated with endocrine disruption of sex hormones and changes to cellular metabolism, such as oxidative stress and epigenetic modifications that affect carcinogenesis [66,67].

Epigenetic modification refers to changes which alter the property of a gene and affect its expression but not its primary DNA sequence. These include changes in DNA methylation, microRNA expression and histone modification. Changes which affect breast development are especially significant, as they can affect breast cancer risk later in life [58].

8.1 In vitro studies

In vitro studies have found that PFAS can act as EDCs, increase oxidative stress and induce epigenetic changes associated with breast carcinogenesis [65,67,68].

Both PFOA and PFOS enhance the effects of oestradiol in human breast cancer cells, leading to increased cellular growth and proliferation [68]. PFOS can induce proliferation, migration and invasion of human breast cells by altering levels of cell-cycle regulatory proteins, partly through the activation of oestrogen receptors [69].

PFOA may promote proliferation, migration and invasion of human breast cells through effects involving PPARα[‡]-dependent pathways, which are associated with anticancer activity and tumour suppression [57,70]. PFOA increases breast cancer cell proliferation at very low (picomole) concentrations only through the MAPK/Erk signalling pathway [71]. An analysis of the molecular pathways involved in PFOA-induced breast cancer using pre-existing datasets, bioinformatics and cellular experiments concluded that PFOA promoted cell migration and invasion in human breast cancer cells through the

[‡]Peroxisome proliferator-activated receptor α (PPARα) regulates genes involved in lipid metabolism and is a major regulator of energy homeostasis and is involved in the regulation of the tumour microenvironment [109].

actions of oestrogen receptors, ERα[§] and GPER[¶], and that activation was likely to be through P13K/Akt and MAPK/Erk signalling pathways, which are associated with cancer metastasis [72].

PFOS and PFOA can induce epigenetic changes, including alterations to DNA methylation, modification of histones and changes to microRNAs in different types of human cells, including embryonic stem cells [67].

Fewer in vitro studies have investigated the effects of emerging PFAS on carcinogenicity. PFOA substitutes, HFPO-DA, HFPO-TA and HFPO-TeA, can bind to oestrogen receptors, ERα and ERβ [73]. HFPO-TA and HFPO-TeA had greater affinity[§] compared to PFOA, whereas HFPO-DA had less affinity. PFOA was weakly oestrogenic, whereas HFPO-TA and HFPO-TeA acted as oestrogen antagonists, and HFPO-DA had no effect.

PFHxS can promote cell proliferation, migration and invasion of breast epithelial cells through the activation of CAR[#] and PPARα pathways [57]. Sixteen legacy and emerging PFAS were examined for their ability to activate PPAR and oestrogen receptors using luciferase gene reporter assays. Most PFAS activated PPARα and PPARγ, with HFPO-DA being the most potent [74]. Only PFHxS, 8:2 FTOH and 6:2 FTOH could activate oestrogen receptors and were weakly oestrogenic.

8.2 Animal studies

Animal studies have shown mammary tissue development may be altered after PFAS exposure in rodents [75,76]. In utero exposure to low concentrations of PFOA can delay development and alter the structure and growth of mammary glands [75] and disrupt lactation [76] in female offspring, which can increase the risk of mammary tumours [77].

Studies in different species have shown PFAS are EDCs which affect oestrogen and other sex hormones. For example, exposure of zebrafish to PFOA, HFPO-TA, HFPO-DA or HFPO-TeA increased synthesis of oestrogen, testosterone and vitellogenin (an oestrogen-responsive biomarker) [73] and PFOA and PFOS exposure in rats increased serum oestradiol levels and protein expression of ERα in the uterus [78].

Legacy and emerging PFAS can be toxic to the immune system. Studies in mammals and birds have found that exposure to several different long-chain PFAS, including PFOS and PFOA, induces oxidative stress, which may damage DNA and promote carcinogenesis (see reviews [7] and [26]). Chronic inflammation or suppression of the immune system may also promote cancer development.

[§]Estrogen receptor alpha (ERα) and beta (ERβ) are nuclear transcription factors activated by oestrogen. ERα activation is responsible for cell proliferation, whilst ERβ has antiproliferative effects.

[¶]G protein-coupled oestrogen receptor (GPER) is a transmembrane receptor implicated in breast cancer metastasis.

[#]Constitutive androstane receptor (CAR) primarily functions in sensing and metabolising xenobiotics. The (over)activation of CAR can promote tumour growth [110].

Immune suppression, including decreased antibody response, has been observed for PFOS, PFOA and HFPO-DA in most rodent studies (see review [79]). Exposure to long-chain PFAS may promote chronic inflammation; for example, exposure of mice to PFDA or PFUnA promotes allergic inflammation [80].

Legacy PFAS can induce epigenetic modifications related to carcinogenesis [7,67]. For example, prenatal exposure of rats to PFOS altered microRNA, which regulates tumour suppressor genes and oncogenes [81], and chronic, low-level exposure to PFOS in mice suppressed the biosynthesis of oestradiol through histone modifications [82]. PFOA exposure to female adult mice decreased global methylation in a dose-dependent manner [83].

8.3 Epidemiological studies

Several studies from different populations have examined whether blood serum levels of PFAS influence breast cancer risk. Most have found elevated levels associated with increased risk [59,84–88]. Studies included relatively small sample sizes, and most were case-control studies.

The first to report that serum levels of PFAS may be linked to breast cancer was a small case-control** study of Greenlandic Inuit women††, which found those with higher serum levels of PFOS, PFOSA and PFHxS were at higher risk of breast cancer [84,88]. A follow-up study in the same population found higher levels of PFOA, PFOS, PFHxS and PFAS mixtures were associated with increased risk, and elevated PFDA and PFNA may also increase risk [85].

Elevated serum levels of PFOS, PFNA, PFHxS, PFDA, and especially PFOA were found to increase breast cancer risk in a dose-dependent manner, based on NHANES data from the US population [86]. In women from the Philippines, elevated levels of PFDoA, PFDA and PFHxA were positively associated with breast cancer risk, with PFDoA having the strongest association [87]. A prospective Chinese study, with an average follow-up time of 9.6 years, measured levels of 12 PFAS and examined their association with breast cancer risk. They found elevated plasma levels of PFOA and PFHpA increased breast cancer risk in a dose-dependent manner [59].

Other studies have found that associations are restricted to breast cancer subtypes [89–93]. By examining exposure to 10 PFAS and breast cancer risk in Taiwanese women under 50, a positive association was found between

** Case control (or retrospective) study is a type of observational study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people without the disease or condition. Case-control studies can establish a correlation, but do not demonstrate causation [111].

†† Greenlandic Inuit women are more susceptible to breast cancer as a result of a higher incidence of BRCA1 gene mutations and polymorphisms in CYP1A1 (encodes cytochrome P450; an enzyme involved in metabolism of environmental chemicals and oestrogen) and CYP17 (encodes aromatase; an enzyme involved in oestrogen biosynthesis) [96].

PFHxS and PFOS exposure and risk of oestrogen receptor-positive (ER+) breast cancer [90]. A US study found no significant association between breast cancer risk and serum levels of PFOS or PFOA. However, it found an increased risk of hormone receptor-positive (HR+) breast cancer for elevated serum PFOS and a possible association with HR- and ER+ breast cancer and elevated serum PFOA [91]. Another US paper reported an association with higher levels of PFHxS and HR- breast cancer, but not other types of breast cancer [92].

There are some reports of an inverse relationship between breast cancer risk and serum levels of PFAS [93–95]. For example, a prospective Danish study, which examined levels of 10 PFAS in pregnant women and risk of breast cancer 10-15 years later, found most PFAS (other than PFOSA) were not associated with breast cancer risk, and PFHxS was inversely associated with risk [94], whilst a Japanese case-control study that examined levels of 20 PFAS found an inverse relationship between most PFAS and breast cancer incidence [95].

Genetic background may influence whether elevated levels of PFAS affect breast cancer [88]. In a group of pregnant Danish women, in which a weak association between elevated PFOSA and breast cancer risk had been demonstrated previously [94], the association was only evident for women who carried specific polymorphisms in genes involved in oestrogen biosynthesis (CYP17 and CYP19) and metabolism (COMT) [96].

Overall, epidemiological studies suggest exposure to PFAS may increase breast cancer risk. Genetic background and breast cancer subtype may impact study outcomes. A 2022 meta-analysis concluded that PFOA and PFHxS are positively associated with breast cancer risk. The same analysis found that PFNA was negatively correlated with risk, and PFOS was not associated with breast cancer [11].

8.4 PFAS exposure and pregnancy

The growth of a baby in utero is mediated by growth factors and hormones, such as oestrogens, progesterone, androgens, insulin and thyroid hormone [58]. In-utero exposure to EDCs can alter breast development, which may increase breast cancer risk later in life [58].

PFAS exposures can alter hormone levels in the placenta. Exposure of placental cells to low levels of PFOS was associated with reduced levels of placental hormones important for breast development, including progesterone, oestradiol, human chorionic gonadotrophin and thyroid hormones [97]. In placental tissue, a positive association between levels of PFUnA, PFNA, PFDA, PFHxS and aromatase (an enzyme involved in oestrogen biosynthesis) has also been reported [98]. Positive associations between cord blood levels of PFOA, PFHxS and oestradiol levels, and PFOS, PFUnA, PFNA and testosterone levels were also described [98].

Animal studies have shown that PFOA

exposure in utero can interfere with normal mammary gland development [99], and an in vitro study found exposure of placental cells to PFOS, PFOA, and HFPO-DA affected gene expression profiles associated with apoptosis, cell growth and proliferation [100].

In newborn babies, legacy and emerging PFAS measured in cord blood have been associated with higher serum levels of sex hormones, including oestrogens [101] and progesterone [102].

In pregnant women, PFAS can affect the levels of different hormones at different stages of pregnancy and in a sex-dependent manner [103]. Higher levels of PFNA and PFDA were associated with higher levels of free testosterone and higher levels of PFHxS were associated with higher levels of testosterone in women carrying male foetuses. In those carrying female foetuses, elevated PFHxS was associated with higher levels of oestradiol and oestriol [103].

Breastfeeding affects levels of PFAS in both mothers and infants. PFOS and PFOA levels are higher in women who have never breastfed and higher in infants who are breastfed [54]. PFAS may be transferred to infants via the placenta and breast milk. Most studies find that higher serum levels of PFOS, PFOA and PFNA are associated with shorter duration of breastfeeding [53]. The longer a woman breastfeeds, the more her risk of breast cancer is reduced [104]. PFAS exposure may also affect the quality of breast milk. A small study found that higher exposure to PFOA, PFHxS, PFNA, PFDA and two PFOS isomers in pregnant women reduced total lipid content and changed the phospholipid composition of breast milk, reducing nutritional quality [105].

9. How are PFAS regulated in the UK?

PFOS[§§] and PFOA are restricted in the UK under the persistent organic pollutant regulation [1,15].

Most chemical substances that are manufactured in or imported into Great Britain are regulated by UK REACH. These regulations were based on EU REACH and, since January 2021, have operated independently. EU REACH regulation applies to substances manufactured in or imported into Northern Ireland [1]. A summary of EU PFAS regulations can be found here.

Under REACH, substances may be identified as substances of very high concern (SVHCs) if they meet one or more specific hazard criteria. In the UK, several PFAS are classified as SVHCs. This restricts their manufacture and use.

Currently, there are no PFAS on the UK REACH Authorisation list; however, the following PFAS are identified as SVHCs and are on the UK REACH Candidate List [1]:

- PFOA and its ammonium salt
- C9-C10 PFCAs and their ammonium and sodium salts
- C11-C14 PFCAs
- PFHxS and its salts

[§§] Restrictions apply to PFOS, its salts and PFOSF & PFOA, its salts and PFOA-related compounds.

- HFPO-DA, its salts and its acyl halides
- PFBS and its salts

PFAS regulation in the UK is currently under review. In April 2023, the UK's Health and Safety Executive and Environment Agency published a Regulatory Management Options Analysis (RMOA) for PFAS [1]. Recommendations included limiting the use of PFAS-containing fire-fighting foams and restricting the use of PFAS in textiles, furniture, and cleaning products. Risk assessment and legislative proposals for regulatory action will be set out in the UK REACH Rolling Action Plan in 2024-2025 [106].

Currently, there are no statutory standards for PFAS in drinking water in England and Wales [107]. The Drinking Water Inspectorate guidance requires water companies to monitor PFAS, with a guideline value of 100ng/l. In Scotland, the Drinking Water Quality Regulator has a standard of 100 ng/l for the sum of 20 specified PFAS [1]. The EU has a legal limit of 100 ng/l for the sum of 20 specified PFAS [107].

In surface waters, PFOS has been classed as a priority hazardous substance, with set annual average limits of 0.65 ng/L in water columns and 9.1 µg/kg wet weight (fish) in biota. PFOS is considered a priority hazardous substance in groundwater, although no limits have been set.

At present, there are no specific restrictions on PFAS in food or food contact materials [1]. In contrast, the EU has set legal limits for PFOA, PFOS, PFNA and PFHxS levels in certain foods [108].

Some fluorine gases that belong to PFAS are restricted under the Fluorinated Greenhouse Gases Regulations based on their high global warming potential [1].

The EU has proposed a group restriction for all PFAS (see here). Breast Cancer UK supports this approach and is working with other UK Non-Governmental Organizations (NGOs), calling for a ban on all PFAS in consumer products by 2025, followed by a ban on all PFAS chemicals by 2030 (see here).

10. Conclusions

PFAS comprise a large group of versatile organofluorine compounds used globally for many decades in industrial and consumer products. They are toxic, highly persistent, and ubiquitous in body fluids and tissues of wildlife and humans. Chronic exposure to legacy PFAS has been linked to various health conditions, including reduced fertility, reduced ability to fight infection, thyroid disease and cancer [5]. Evidence increasingly suggests that exposure to emerging PFAS is also harmful.

PFAS may also increase breast cancer risk. Most are EDCs that interfere with oestrogen pathways and/or PPAR [74]; some induce oxidative stress and chronic inflammation, and some may cause epigenetic modifications associated with carcinogenesis [7]. Animal studies suggest that in-utero exposure to PFAS may affect breast development, which could increase susceptibility to breast cancer later in

life [75]. In humans, higher levels of serum PFOA and PFHxS are linked to increased breast cancer risk [11], and some reports suggest emerging PFAS, such as PFHpA, may also affect risk [59].

Humans are exposed to mixtures of PFAS throughout their lives. These effects are not well understood, although some reports demonstrate that PFAS mixtures show additive effects [63,64]. Most people alive today will have been exposed to PFAS throughout their lives, including in utero, and will contain mixtures of different PFAS (and other EDCs) in their blood and tissues [4]. The result of this exposure is unclear. A lack of a control population with no PFAS exposure means it will be challenging to robustly demonstrate if individual PFAS are associated with an increased risk of diseases such as breast cancer.

PFAS may persist in the environment longer than any other synthetic chemical [3]. In light of this, the EU has proposed a class restriction on all PFAS [3]. Some PFAS producers and companies that use PFAS have already announced their intention to stop manufacturing or using these substances [109].

A group restriction of all non-essential uses of PFAS would be a good first step in reducing the damaging effects these compounds have on human health and the environment. Breast Cancer UK supports a ban on all non-essential use of PFAS.

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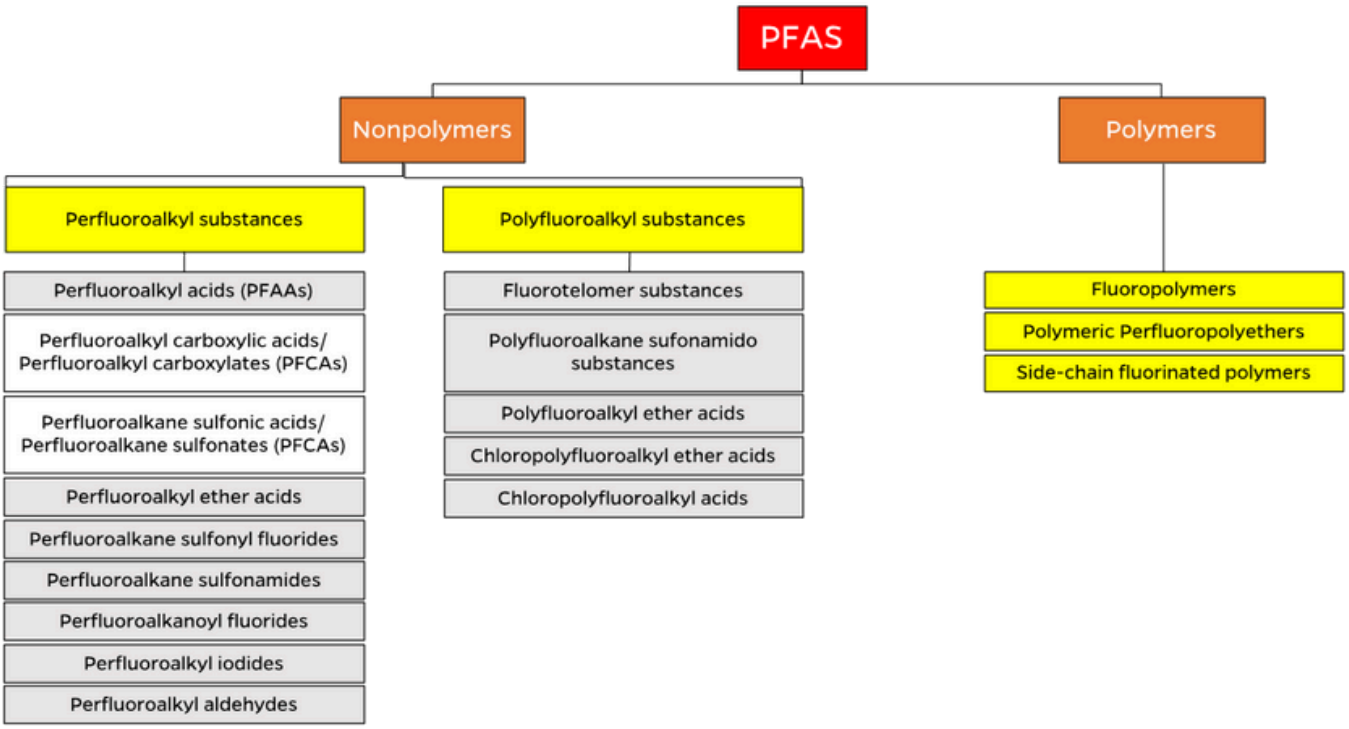
Appendix

Appendix 1. PFAS groupings [113]



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Who we are?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk

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